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FREEDOM OF INFORMATION SUMMARY

NADA 141-178

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste

"...for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona."

Sponsored by:

IDEXX Pharmaceuticals, Inc. Greensboro, NC 27410

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1. GENERAL INFORMATION:

a. File Number:

NADA 141-178

b. Sponsor:

IDEXX Pharmaceuticals, Inc. 4249-105 Piedmont Pkwy Greensboro, NC 27410

Drug Labeler Code: 065274

c. Established Name:

nitazoxanide

d. Proprietary Name:

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste

e. Dosage Form:

Oral Paste

f. How Supplied:

NAVIGATOR Antiprotozoal Oral Paste is supplied in a plastic oral-dose syringe which contains 85 grams of paste. Each gram of paste contains 320 mg of nitazoxanide (32% w/w). Syringes are fitted with a dosage ring designed to deliver 22.72 mg of nitazoxanide/lb, and are marked for a horse weighing up to 1,200 pounds. The NAVIGATOR Antiprotozoal Oral Paste dispensing box contains 26 syringes which provide sufficient paste to treat one 1,200 pound horse for 28 days (5 days at

11.36 mg/lb and 23 days at 22.72 mg/lb).

g. How Dispensed:

 $\mathbf{R}\mathbf{x}$

h. Amount of Active

Ingredients:

Each syringe contains 27.2 g of nitazoxanide

i. Route of Administration:

Oral

Species:

Equine

k. Recommended dosage:

Always provide the Client Information Sheet to the animal owner or person treating the horse with each prescription. NAVIGATOR Antiprotozoal Oral Paste should be administered orally once a day for 28 days as follows:

Days of Administration	Target Dose
Days 1-5	11.36 mg/lb body weight
Days 6-28	22.72 mg/lb body weight

NOTE: A total of 26 syringes are included in the

NAVIGATOR Antiprotozoal Oral Paste dispensing box. The three syringes in the first three spaces will be used to dose the horse for days 1-5. The remaining 23 syringes will dose the horse for days 6-28. The dose is 11.36 mg/lb for the first five (5) days, and 22.72 mg/lb for days 6-28.

Nitazoxanide has not been evaluated in horses that weigh more than 1,200 pounds.

1. Pharmacological Category: Antiprotozoal

m. Indications: NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste

in indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

2. EFFECTIVENESS:

a. Dosage Characterization:

Starting Dose: The 11.36 mg/lb dose is used for days 1-5 to allow for a slower kill of the protozoal microorganisms and allow the horse time to accommodate to any change that may occur in the intestinal flora. Starting the horse at a dose of 22.72 mg/lb may produce a "treatment crisis," which is a worsening of neurological signs, elevated body temperature, decreased appetite and lethargy, presumably due to the rapid kill of protozoal microorganisms.

Pharmacokinetics: Eight (4 males, 4 females) mixed-breed, healthy horses received either a single dose or multiple doses of NAVIGATOR Antiprotozoal Oral Paste formulation for seven consecutive days. Nitazoxanide is rapidly metabolized to the active metabolite, deacetylnitazoxanide. Plasma drug levels of deacetylnitazoxanide were non-detectable by 24 hours post-dosing. According to a validated method, the limit of detection (LOD) was estimated to be 0.015 ppm and the lower limit of quantification (LOQ) was 0.02 ppm. The data from the pharmacokinetic study are presented in the following table:

Table 1. Pharmacokinetic Parameters Determined by Single and Multiple Doses (7) of NAVIGATOR Antiprotozoal Oral Paste in Healthy Horses (mean ± SD, N=8)

Dose (22.72 mg/lb)	C _{max} (ppm)	T _{max} (hrs)	AUC _{0-LOQ} (ppm•hrs)
Single	0.51 ± 0.30	2.13 ± 1.13	1.913 ± 0.53
Multiple	0.97 ± 0.49	3.250 ± 3.57	4.770 ± 2.78

C_{max} (Maximum concentration of deacetylnitazoxanide achieved)

T_{max} (Time maximum concentration was achieved)

AUC_{0-LOQ} (Area Under the Curve from time 0 through the last sample with deacetylnitazoxanide concentration above the LOQ)

Based on the C_{MAX} and AUC values of the single and multiple doses, some accumulation occurs. When comparing the individual pharmacokinetic data (C_{max} , T_{max} , AUC) across the study days and based on the mean standard deviations for each value, there was intersubject variability in the rate and extent of product disposition.

Cell Culture Data: Experiments conducted in cell culture¹ showed that dosages of 1.0 ppm or greater prevented measurable monolayer destruction in a lesion based microassay against developing *Sarcocystis neurona* merozoites (SN-3 strain). In this assay, the concentration of nitazoxanide that inhibited the merozoites by 50% (inhibitory concentration 50; IC₅₀) was 0.52 ppm.

Conclusion: The C_{max} for deacetylnitazoxanide after multiple doses of the 22.72 mg/lb dose was 0.97 ppm (1.9X the IC₅₀ of 0.52 ppm). These data predict that the concentrations of deacetylnitazoxanide in the plasma would reach therapeutic levels against *S. neurona* over the 28-day dosing period. The 28-day course of therapy was selected based on the pharmacokinetics of the drug and the life cycle of the organism. The merozoites develop in a 10-14 day period after ingestion of the oocysts. The 28-day course of therapy is roughly twice the length of this life cycle to help ensure that the protozoal organism is controlled before therapy is discontinued.

¹ Lindsay, D.S., Zhang, Y., Dubey, J.P., et al. Determination of the activity of nitazoxanide against *Sarcocystis neurona* in cell cultures, in Proceedings of the American Association of Veterinary Parasitology 43rd Annual Meeting, 1998:44.

b. Substantial Evidence:

(1) Historical Control:

EPM is usually a progressive neurological disease. It has been estimated that up to 55-65%² of horses respond favorably to treatment. However, it is further estimated that no more than 10% of treated horses recover completely. One of the most important points to consider is that EPM produces highly variable clinical disease. Historical controls were used in the field studies because, without treatment EPM is usually a progressive disease. At the time these studies were conducted, there was no FDA approved treatment for EPM. The use of historical controls in the evaluation of compounds for effectiveness is described in 21 CFR 514.117(b)(4)(iv).

(2) Field Study I:

This field study was conducted at thirteen sites, geographically distributed across the United States.

(a) Participating Investigators:

Robert Buell, DVM	G. David McCarroll, DVM
Hialeah, FL	Goldsby, OK
Gary Doxtater, DVM	Dawn Mrad, DVM
Williamsburg, VA	Wentzville, MO
Diane Finch, DVM	Thomas Schwerbrock, DVM
Ft. Wayne, IN	Kewanee, IL
Karen Flipse, DVM	Bruce Sickels, DVM
Vass, NC	Union City, IN
L. Mark Haugland, DVM Conroe, TX	Nicholas Vatistas, BVSc, PhD, MRCVS Vacaville, CA
Richard Henninger, DVM	Wesley Williams, DVM
Findlay, OH	Irving, TX

² Granstrom DE. *Understanding Equine Protozoal Myeloencephalitis*: Your Guide to Horse Health Care and Management. Lexington: The Blood-Horse Inc, 1997:10.

Michael Major, DVM Edmond, OK

- (b) Study Design: NAVIGATOR Antiprotozoal Oral Paste was administered once a day for five days at 11.36 mg/lb and then once a day for 23 days at 22.72 mg/lb. The effectiveness of NAVIGATOR Antiprotozoal Oral Paste for treating EPM was evaluated by a standardized neurological examination and Western blot (WB) assay of the cerebral spinal fluid (CSF). All investigators were trained to conduct a standardized neurological examination using sample cases that had been videotaped by the sponsor.
- (c) Variables Evaluated: Investigators performed the neurological examination on each horse prior to initiation of dosing (Day 0), on Day 28 (last day of dosing) and Day 85 (57 days post dosing). The Day 85 evaluation was the critical endpoint. After performing the neurological examination, the investigator assigned a grade or fraction of a grade to each horse based on the modified Mayhew scale:
 - 0 = no gait deficits,
 - 1 = deficits barely perceptible, worsened with head elevation,
 - 2 = deficits noted at a walk,
 - 3 = deficits noted at rest and walking; nearly falls with head elevation,
 - 4 = falls or nearly falls at normal gait,
 - 5 = recumbent patient.

In order to be considered a success by the investigator, a horse had to improve at least one grade on the modified Mayhew scale by Day 85 and/or have a negative result from a Western blot assay of the CSF by Day 85.

The neurological examination was also videotaped (Day 0, Day 28, Day 85) for each horse. A separate videotape was used for each neurological examination on a horse. In order to accomplish objectivity and corroborate the investigator's evaluation, three independent equine experts reviewed and graded each videotape. The experts were masked to the date and the identification of the horse while reviewing each tape. If two or more of the three experts indicated that the horse improved any amount, then the case was considered a "corroborated" success.

All horses entered the study with a positive CSF Western blot assay for *S. neurona* and with grade 2 to 4 asymmetric spinal ataxia or grade 1 spinal ataxia if accompanied by muscle atrophy or cranial nerve deficits.

NAVIGATOR Antiprotozoal Oral Paste was used concomitantly with other medications including anthelmintics, antibiotics, non-steroidal and steroidal anti-inflammatory agents, diuretics, tranquilizers and vaccines.

(d) Results: Ninety-six (96) horses were enrolled into the study and 47 were excluded from the analysis of effectiveness for various reasons. Forty-nine (49) horses were included in the analysis. The following tables describe the patient population:

Table 2. Study Population by Age

Age	Number (%)
1 - 5 years	18 (37%)
>5 – 10 years	16 (33%)
>10 - 15 years	8 (16%)
>15 - 20 years	5 (10%)
>20 - 25 years	2 (4%)
Total	49 (100%)

Table 3. Study Population by Sex

Sex	Number (%)	
Stallion	3 (6%)	
Gelding	25 (51%)	
Mare	21 (43%)	
Total	49 (100%)	

Table 4. Study Population by Breed

Breed	Number (%)
Arabian	1 (2%)
Hanoverian	2 (4%)
Missouri Fox Trotter	1 (2%)
Paint	4 (8%)
Paso Fino	1 (2%)
Peruvian Paso	1 (2%)
Quarter Horse	14 (29%)
Quarter Horse X	3 (6%)
Standardbred	2 (4%)
Thoroughbred	14 (29%)
Thoroughbred X	3 (6%)
Warmblood	2 (4%)
Westphalian	1 (2%)
Total	49 (100%)

Based on the investigators' clinical evaluations and the results of the CSF analyses, 28/49 (57%) of the cases were considered "successes." Seven of the 49 horses (14%), had a negative result from a Western blot assay of the CSF collected on Day 85. Three of the 49 horses (6%) treated with NAVIGATOR Paste in the study achieved Grade 0 (clinically normal) at Day 85.

In order to corroborate the cases deemed successful by the clinical investigator, equine experts reviewed the videotapes of the success cases in a masked fashion. A horse whose CSF Western Blot converted to negative, was deemed a success and was not reviewed by the experts. Based on the corroboration of the experts' scores, 22 of 49 horses (45%) had an improved neurological examination on Day 85 and/or a negative result from a Western blot assay of the CSF collected on Day 85. Seven of the 22 horses (32%) evaluated as successes had a negative result from a Western blot assay of the CSF collected on Day 85.

Results of the effectiveness scores from the clinical investigators and corroboration by the equine experts are shown below:

Table 5. Effectiveness Results from the Clinical Investigators and Equine Experts in Field Study I.		
	Number of Successes	Percent
Cases rated as Successes by Investigators	20/10	
	28/49	57.1%
-Cases not corroborated by experts		
	-6	
Total Number of Corroborated Successes	22/49	44.9%

Adverse reactions were observed in this field study and are described in Section 3 of this FOI Summary.

Based on the investigators' clinical evaluations and the results of the CSF analyses, 28/49 (57%) of the cases were considered "successes." Seven of the 49 horses (14%), had a negative result from a Western blot assay of the CSF collected on Day 85. Three of the 49 horses (6%) treated with NAVIGATOR Antiprotozoal Oral Paste in the study achieved Grade 0 (clinically normal) at Day 85.

Twenty-two of 49 horses (45%) had improved neurological examinations on Day 85 and/or a negative result from a Western blot assay of the CSF collected on Day 85. Seven of the 22 horses (32%) evaluated as successes had a negative result from a Western blot assay of the CSF collected on Day 85.

Adverse reactions were observed in this field study and are described in Section 3 (Target Animal Safety) of this FOI Summary.

(3) Field Study II:

(a) Study Design: This study was designed to obtain additional effectiveness and safety data. Basic information was collected about the response to therapy. CSF collection and analysis were not requirements of this study. Four-hundred-nineteen (419) horses from 150 clinical investigators were enrolled in the study. Two hundred fifty horses completed the study and provided complete results of the treatment. The protocol consisted of documenting the diagnosis of EPM, treating with nitazoxanide and documenting the neurological abnormalities. Investigators were not required to videotape the neurological examinations.

For 46 horses (18%), treatment was administered once a day for 28 days using a dose of 22.72 mg/lb for the entire treatment period. For 204 horses (82%), treatment was comprised of a graduated dose of 11.36 mg/lb once a day for five or six days, followed by a dose of 22.72 mg/lb once a day for 22 or 23 days.

- (b) Variables Evaluated: Investigators performed the neurological examination on each horse prior to initiation of dosing (Day 0), and approximately 85 days after beginning nitazoxanide therapy. CSF was obtained whenever possible. Many owners and veterinarians declined to collect the post-treatment CSF sample in view of the magnitude of the horses' neurological improvement and the inherent risks associated with the collection procedure.
- (c) Results: Nitazoxanide administration was interrupted in 24 cases during this field study (58% of these cases were reported by one investigator). Five of these cases were treated with 22.72 mg/lb beginning on day 1 and the remaining 19 cases received nitazoxanide according to the graduated dosage regimen. An elevated body temperature was observed in each instance. Interruption of nitazoxanide administration occurred within the first nine days in 75% of these cases, and the median duration that a horse did not receive nitazoxanide was two days. In two cases, nitazoxanide administration was interrupted again on treatment days 15 and 22, respectively.

Success was based upon the same criteria used for the investigators in the first field study, i.e., one full grade improvement on neurological examination and/or a negative CSF-WB on study Day 85. Of the horses that completed the study, eighty-one percent (81%) were considered successes.

Table 6. Effectiveness Results from the Investigators in Field Study II

	N = cases	Percent
Complete Cases	250	(
Success	203	81%
Failure	47	19%
Incomplete Cases	169	(
Total Cases	419	

One hundred-fifteen (115) of the 250 horses had been previously treated for EPM with other therapies. Seventy-eight percent (90/115) of these were successfully treated with nitazoxanide.

Thirty-eight of the 188 (20%) receiving follow-up spinal centesis had a negative result from the Western blot assay of the CSF. Forty-seven (19%) of the 250 horses completing the study, were considered failures.

Adverse reactions were observed in this field study and are described in Section 3 of this FOI Summary.

(4) Conclusions of field effectiveness studies:

In the field studies, 299 horses completed the 28 day treatment. Clinical effectiveness based upon a negative CSF tap or improvement in the neurological condition of the horse was 57% in Field Study I and 81% in Field Study II.

Adverse reactions did occur in these studies and are discussed in Section 3 (Target Animal Safety) of this FOI Summary.

3. TARGET ANIMAL SAFETY:

a. Tolerance Study:

(1) Type of Study:

Tolerance Study

(2) Study Director:

John W. Campbell, Ph.D. Southwest Bio-Labs, Inc.

Las Cruces, NM

(3) General Design:

- (a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.
- (b) Purpose: The purpose of this study was to define the toxic signs associated with a single administration of an elevated dose of nitazoxanide.
- (c) Test Animal Allocation and Drug Administration: Eight horses were given one dose of 113.64 mg/lb (which is 10X the starting dose of 11.36 mg/lb or 5X the regular dose of 22.72 mg/lb) and observed for 14 days.

(4) Results:

- (a) Clinical Findings: Transient depressed appetite, loose stools and lethargy were observed, and lasted from 11 to 14 days post-treatment. One horse developed edema in the legs and received supportive therapy (flunixin meglumine for one day, kaolin pectin for three days) beginning eight days after treatment. No other supportive therapy was administered. All eight horses returned to normal.
- (b) Pathology: Necropsy was not performed.
- (5) Conclusion: The results of this study indicate that a single 113.64 mg/lb dose of NAVIGATOR Antiprotozoal Oral Paste resulted in reversible signs consisting of a depressed appetite, loose stools and lethargy in all eight horses. One of these eight horses required treatment for edema in the legs.

b. Toxicity Study I:

(1) Type of Study:

Toxicity Study

(2) Study Director:

John W. Campbell, Ph.D.

Southwest Bio-Labs, Inc.

Las Cruces, NM

(3) General Design:

- (a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.
- (b) Purpose: The purpose of this study was to define the safety margin of the product at various dosages.

(c) Test Animal Allocation and Drug Administration:

Table 7. Dosage Rate in NAVIGATOR Antiprotozoal Oral Paste Toxicity Study I

Group (4M, 4F)	Duration	Daily Dosage	Average Group Dosage Rate
1	60 DAYS	Placebo (sham dosed)	0
2	60 DAYS	1 syringe NAVIGATOR	28.18 mg/lb
3	60 DAYS	2 syringes NAVIGATOR	57.27 mg/lb
4	4 DAYS	4 syringes NAVIGATOR	110.91 mg/lb
	7 DAYS	1 syringe NAVIGATOR	28.18 mg/lb
5	7 DAYS	2 syringes NAVIGATOR	57.27 mg/lb
	60 DAYS	3 syringes NAVIGATOR	78.18 mg/lb

All horses were observed for seven days after the last treatment. There were eight horses per group.

(4) Results:

(a) Clinical Findings:

- 1 In Group 1 (Placebo), none of the eight horses experienced any adverse clinical signs.
- 2 In Group 2 (28.18 mg/lb, 1.2X regular dose), all eight horses completed the study. Three horses showed no adverse reactions during the study period. Four of the horses developed a mild, transient, depressed appetite between Days 4 and 15 of the study. Three of the horses became lethargic at some time between Days 4 and 8 of the study. Two of the Group 2 horses voided loose stools periodically between Days 6 and 36 of the study. All eight horses in Group 2 recovered without therapeutic intervention.
- In Group 3 (57.27 mg/lb, 2.5X regular dose), six horses completed the study. Seven of the horses developed a mild, depressed appetite periodically during the study period, beginning on Day 4. All eight horses were occasionally lethargic during the study, beginning on Day 3. Four of the Group 3 horses voided loose stools periodically during the study period beginning on Days 4 through 64. Two of the horses in Group 3 developed severe clinical signs and died after being dosed for 15 days and 37 days, respectively. The cause of death for both horses was severe erosion and ulceration of the colon. Two horses received supportive therapy after nitazoxanide treatment ended (lactated Ringers solution for

- 6-10 days, kaolin pectin for 0-7 days, a potentiated sulfonamide for 0-3 days, and flunixin meglumine for 0-2 days) and one died. The remaining horses survived without therapeutic intervention.
- 4 In Group 4 (110.91 mg/lb, 4.9X regular dose), dosing was discontinued on Day 4 because horses in this treatment group developed severe clinical signs (anorexia, diarrhea and lethargy). All eight horses developed decreased appetite and became lethargic during the first three days of the study. Four of the horses voided loose stools for one day each, during Days 2-5 of the study. Five of the eight horses given the 110.91 mg/lb average daily dose died within the first two to four days of the study. The cause of death in all cases was severe erosion and ulceration of the colon. The three remaining horses recovered after removal from the study on Day 4 and administration of supportive therapy for six days (lactated Ringers, carafate, kaolin pectin). They also received a 12-day course of a potentiated sulfonamide.
- 5 In Group 5, horses were dosed with the contents of one syringe per day for one week, two syringes per day for a second week and then three syringes per day for an additional 60 days (average maximum dose 78.18 mg/lb, 3.4X regular dose). All eight horses developed decreased appetite and were periodically lethargic, beginning as early as Day 4. Four horses periodically voided loose feces beginning on Days 9-23. Five horses successfully completed this dosage regimen without therapeutic intervention. Three horses demonstrated clinical signs of drug toxicity and were removed from the study on Days 17 through 31. They developed significant weight loss, anorexia, lethargy, and decreased gut sounds. These three horses recovered with supportive therapy (lactated Ringers solution, kaolin pectin, and potentiated sulfonamide). Twenty-three days later, one horse developed gastroenteritis complicated by Salmonellosis and died.
- (b) Clinical Pathology: During this study there were numerous findings of elevated or depressed cellular elements in the hemogram. Similarly, erratic changes in clinical chemistry were observed, but no dose response was established. Although statistical analysis failed to demonstrate a dose response, some of the findings were present in horses that were affected by severe gastrointestinal illness, and thus are indirectly related to nitazoxanide toxicity. Hypoproteinemia was occasionally observed in horses in the higher dosage groups and was likely associated with a protein losing enteropathy. Several hemograms demonstrated a stress leukogram, which is consistent with the degree of toxicity observed in this study.

- (c) Post-mortem Pathology: Gross and histopathological examination of animals that died on the study indicates the colon as the target tissue. In animals with severe colonic lesions (ulcerations, erosions), the stomach, small intestine and cecum were also affected; but to a lesser degree. No treatment-related effects on other tissues were noted in study animals.
- (5) Conclusions: This study demonstrated that administration of one entire syringe of NAVIGATOR Antiprotozoal Oral Paste (average dose of 28.18 mg/lb) resulted in signs of toxicity consisting of a mild, depressed appetite, lethargy and loose feces. When two syringes were administered, the same toxicity was noted and in addition, two horses died due to severe erosion and ulceration of the colon. Doses exceeding two syringes/horse/day were not tolerated.

c. Toxicity Study II:

(1) Type of Study:

Toxicity Study

(2) Study Director:

Wendy K. Rowland, MS

Johnson Research, LLC

Parma, ID

(3) General Design:

- (a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.
- (b) Purpose: The purpose of this study was to clearly define the safety of the product at the recommended dosage.
- (c) Test Animal Allocation and Drug Administration:

Table 8. Dosage Rate in NAVIGATOR Antiprotozoal Oral Paste Toxicity Study II

Group(4M, 4F)	Duration	Daily Dosage	Group Description
1	28 DAYS	sham dosed	Placebo
2	28 DAYS	11.36 mg/lb days 1-5, 22.72 mg/lb days 6-28	1X Group
3	28 DAYS	22.72 mg/lb days 1-5, 45.45 mg/lb days 6-28	2X Group

All horses were observed for seven days after the last treatment. There were eight horses in each treatment group.

(4) Results:

- (a) Clinical Findings: All horses in all groups completed the dosing portion of the study.
 - In Group 1 (Placebo), four of the horses showed decreased appetite on at least one day of the study. Three horses voided loose stools or had limb or ventral edema on at least one day of the study. Two horses voided discolored brown (normal color was green) feces. Four horses produced malodorous feces during the study. Four horses had no clinical findings during the study. One horse lost weight, but the group gained an average of 43 pounds during the study.
 - 2 In Group 2 (1X group), one of the horses showed decreased appetite and had limb edema occasionally during the study. Three horses voided loose feces on at least one day of the study. Two horses voided discolored brown feces. Two other horses produced malodorous feces during the study. Four horses had no clinical findings during the study. No horses lost weight, and the group gained an average of 61 pounds during the study. These horses gained more weight during the study than any other group.
 - 3 In Group 3 (2X group), eight horses had decreased appetite during the study period. Five horses became lethargic during the study. All eight horses had loose and malodorous feces on at least one day during the study period. Four horses had discolored brown or black feces. Five horses developed limb or ventral edema during the study. Three horses in Group 3 developed fever for at least one day during the study period. One was treated with hydrotherapy for three days and another horse was given five days of oral electrolytes. One horse in Group 3 developed enterocolitis near the end of the study period and was given supportive therapy including antibiotics, flunixin meglumine, kaolin pectin, IV fluids, omeprazole and carafate. It was euthanized at the end of the study. Diagnostic testing, complete necropsy and histopathology revealed findings consistent with alteration of gut microflora, enterocolitis and Salmonellosis in this horse.

Three horses in Group 3 lost weight, but the group gained an average of two pounds during the study. Of the seven horses alive at the end of the study, four were normal, and three were observed for an additional 15

days. These three horses had low serum albumin (1/3), low serum total protein (2/3) or leukocytosis (3/3) at the end of the study. Two of these three horses also had lost weight over the course of the study. All three horses were rechecked eight and 15 days later and had returned to normal at the 15 day recheck without therapeutic intervention.

(b) Clinical Pathology:

Statistical Analysis Methods: Variables measured only once following treatment were analyzed using analysis of covariance (ANCOVA). Variables measured multiple times following treatment were analyzed using repeated measures ANCOVA. The covariate in both cases was the baseline value of the variable, if measured only once pre-treatment, or the average of two baseline values closest to the initiation of treatment.

Treatment and treatment by time interactions (in the repeated measures analysis) were tested at an alpha level of 0.10. If the time by treatment interaction was significant, treatment groups were compared to control at each measurement time. Otherwise, if the treatment group effect was significant, treatment groups were compared to control, averaged over time. If gender by treatment interaction was significant at the 0.05 level, the analysis was performed separately for each sex and followed the same logic for testing treatment effects as the above.

Combined Sexes Analyses: There were statistically significant effects of the 2X dose that exhibited during the study in the following variables: absolute segmented neutrophils and white blood cells were elevated on days 15 and 35; albumin was decreased on days 22, 29 and 35; eosinophils were decreased on days 22 and 35 (1X group was also decreased on days 4 and 15); and globulin was decreased on days 8, 15, 22, 29 and 35. Differential white blood cell percentages revealed a statistically significant increase in neutrophils and monocytes and a decrease in lymphocytes when averaged over all observation times. The changes in these variables were consistent with the clinical findings.

Separate Sexes Analyses: There were effects of the 2X dose near the end of the study in AST, BUN, prothrombin time and total protein. In females, AST was reduced on days 22 and 35. In males, BUN was reduced on days 4, 15, 25 and 35. In males, prothrombin time was reduced on days 4 and 35. Total protein was reduced on days 29 and 35 in females, and on days 15 and 29 in males. ALT, calcium, and creatine kinase at the 2X dose were significantly lower than control, averaged over

all times, in males only. There was no clinical significance of these changes, with exception of the lowered total protein.

Urinalysis values were all within the normal reference range, but the average urine pH was significantly lower in the 2X dose group than in the other groups. Water consumption in the 2X group horses was elevated pre-study and remained so throughout the study period.

- (c) Post-mortem Pathology: Necropsy was not performed.
- (5) Conclusions: This study demonstrated that administration of NAVIGATOR Antiprotozoal Oral Paste, when administered according to label directions (11.36 mg/lb for Days 1-5 followed by 22.72 mg/lb for Days 6-28, is safe for use in healthy horses. Conversely, 22.72 mg/lb for Days 1-5 followed by 45.45 mg/lb for Days 6-28, can result in irreversible, fatal enterocolitis despite supportive therapy.

d. Field Safety Evaluation:

(1) Field Study I:

In this field study, a total of 81 horses received at least one dose of nitazoxanide. Twenty-two horses (27%) experienced adverse reactions as noted in the table on page 17:

Table 9. Adverse Reactions in Field Study I

Body System	Adverse Reactions	% Incidence in First Field Study (n ¹ /81)
Total	Auverse Reactions	27% (22/81)
Alimentary and Urinary	Anorexia	2 (2/81)
Annichtary and Crimary	Reduced appetite	9 (7/81)
	Loose feces	0 (0/81)
	Discolored ² urine or	1 (1/81)
	discolored ³ , malodorous feces	
	Colic	2 (2/81)
	Diarrhea	2 (2/81)
	Hematuria, stranguria	1 (1/81)
Circulatory	Shock	0 (0/81)
	Elevated Heart Rate &	1 (1/81)
	Respiration Rate	
lemolymphatic	Fever	12 (10/81)
• •	Edematous limbs	7 (6/81)
	Lymphadenopathy	0 (0/81)
	Leukopenia	0 (0/81)
	Facial Edema	0 (0/81)
	Mastitis	0 (0/81)
Musculoskeletal	Sore/warm feet/increased	1 (1/81)
	digital pulses	
	Stiffness	2 (2/81)
	Pastern/joint pain	0 (0/81)
Neurological	Lethargy/depression	9 (7/81)
	Worsening of neurological	4 (3/81)
	signs	
	Behavioral changes	0 (0/81)
Respiratory	Nasal discharge	0 (0/81)

¹Number of horses

Fever, anorexia/reduced appetite and lethargy/depression were the most commonly observed adverse reactions in this study. The following table describes the onset and duration of these adverse reactions.

²Urine color can change to bright orange or dark yellow due to excretion of nitazoxanide in the urine ³Excretion of nitazoxanide in the bile can change feces color from green to brown

Adverse Reaction

[n=animals affected]

[n=a

Table 10. Onset & Duration of Most Common Adverse Reactions in Field Study I

Aside from the adverse reactions that occurred in the horses that died or were euthanized, most were reported as isolated events. In some cases, however, certain adverse reactions occurred together. During this study, fever, lethargy/depression and anorexia/reduced appetite were reported to occur together in 3 cases. Fever and anorexia/reduced appetite were also observed concurrently with worsening of neurological signs (one case) and lethargy/depression and diarrhea (one case). In two cases anorexia/decreased appetite was accompanied by fever and worsening of neurological signs, respectively.

Of the 22 horses in the Field Study I that experienced adverse reactions, six resolved without any therapeutic intervention. The clinical signs in the remaining 16 horses were treated with anti-inflammatory drugs such as dexamethasone, flunixin meglumine, phenylbutazone and DMSO. In some cases, intravenous fluids were also administered.

Four horses were euthanized during this study because of worsening neurological conditions. Three of these horses had necropsy findings consistent with chronic EPM. Two of the four also experienced adverse drug reactions.

¹Two horses were euthanized after 11 and 24 days of neurological worsening; one horse improved after four days

² Bars represent both affected horses; one horse had diarrhea on Day 2 and one horse had diarrhea on Day 3

³ Bars represent both affected horses; one horse was colicky on Day 8 and one was colicky for 1 hour on Day 20

(2) Field Study II:

In this field study, a total of 416 horses received at least one dose of nitazoxanide. One hundred twenty-nine horses (31%) demonstrated an adverse reaction as noted in the following table.

Table 11. Adverse Reactions in the Field Study II

Body System	Adverse Reactions	% Incidence in Field Study II (n¹/416)
Total		31% (129/416)
Alimentary and	Anorexia	14 (59/416) ²
Urinary	Reduced appetite	
	Loose feces	3 (14/416)
	Discolored ³ urine or discolored ⁴ ,	3 (12/416)
	malodorous feces	
	Colic	2 (8/416)
	Diarrhea	1 (6/416)
	Hematuria, stranguria	0 (0/416)
Circulatory	Shock	<1 (1/416)
	Elevated Heart Rate & Respiration	0 (0/416)
	Rate	
Hemolymphatic	Fever	14 (57/416)
	Edematous limbs	5 (19/416)
	Lymphadenopathy	<1 (2/416)
	Leukopenia	<1 (2/416)
	Facial Edema	<1 (2/416)
	Mastitis	<1 (1/416)
Musculoskeletal	Sore/warm feet/increased digital	2 (10/416)
	pulses	•
	Stiffness	<1 (2/416)
	Pastern/joint pain	<1 (1/416)
Neurological	Lethargy/depression	10 (40/416)
-	Worsening of neurological signs	2 (9/416)
	Behavioral changes	<1 (2/416)
Respiratory	Nasal discharge	<1 (1/416)

¹ Number of horses

Fever, anorexia/reduced appetite and lethargy/depression were the most commonly observed adverse reactions in this study. The following table describes the onset and duration of these adverse reactions.

² Horses with anorexia and reduced appetite were combined in this study

³ Urine color can change to bright orange or dark yellow due to excretion of nitazoxanide in the urine

⁴ Excretion of nitazoxanide in the bile can change feces color from green to brown

Adverse Reaction Day of Treatment 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 (n=animals affected) n=57, median duration 2 days of Affected Horses Anorexia / Reduced Appetite n=59, median duration 4 days Lethargy / Depression 1=39, median duration 6 days Neurological Worsening n=10, median duration 4 days Loose Feces / Diarrhea n=20, median duration 2 days Colic n=8, median duration 2 days

Table 12. Onset & Duration of Most Common Adverse Reactions in Field Study II

Six of the eight (75%) horses experienced the onset of colic over the range of the first nine days of the study.

During this field study, anorexia/reduced appetite and lethargy/depression were concurrently reported in four cases. In three of these four cases the clinical signs were also accompanied by loose feces/diarrhea. One febrile horse demonstrated anorexia/reduced appetite along with loose feces/diarrhea and another febrile horse had anorexia/depressed appetite with lethargy/depression and lymphadenopathy. Other adverse reactions were reported as isolated events.

Clinical signs resolved without any therapeutic intervention in 44 of the 129 horses that showed adverse reactions. The remaining 85 horses were managed with anti-inflammatory agents or combination therapy comprised of an anti-inflammatory agent and another class of drug. For example, four of 40 horses demonstrating lethargy/depression were treated with flunixin meglumine, phenylbutazone, dexamethasone, DMSO, ceftiofur, and folic acid. Fever was managed in 19 of 57 horses with flunixin meglumine. phenylbutazone, dexamethasone, and gentamicin. Anorexic horses received flunixin meglumine, dexamethasone, cimetidine, and mineral oil in six of 59 cases. Eight of 21 horses demonstrating edema were treated with flunixin meglumine, phenylbutazone, furosemide, procaine penicillin, trimethoprim sulfa, and bran mash. Six of ten horses with increased digital pulses and sore/warm feet received flunixin meglumine, phenylbutazone, and topical nitroglycerin. Colic was treated with flunixin meglumine, mineral oil, bismuth subsalicylate, and IV fluids in six of the eight cases. Four of nine horses demonstrating neurological worsening received flunixin meglumine, dexamethasone, DMSO, detomidine, and Vitamin E. Various treatment regimens (dosage and combination) were utilized but most were administered for brief periods of time due to rapid resolution of clinical signs. No adjunctive therapy was administered to horses with loose feces or diarrhea. In addition to the previously mentioned treatments, administration of nitazoxanide was interrupted in 24 febrile horses. The median duration that a horse did not receive nitazoxanide was two days.

Twenty-eight horses died or were euthanized during Field Study II. Five of these cases were possibly associated with the use of nitazoxanide and are summarized below

One horse became febrile (103°F) on Day 8 of the study and nitazoxanide was stopped. The fever worsened (106°F) and projectile diarrhea developed. The horse was euthanized on Day 11 of the study. Necropsy revealed acute bacterial typhlocolitis. Another horse exhibited lethargy and anorexia on Day 2 of the study, but continued to receive nitazoxanide. On Day 7 of the study, the horse developed diarrhea and on Day 8 developed a fever of 104°F. Despite stopping nitazoxanide and transfer to a referral hospital, the horse died on Day 16. Necropsy revealed fibronecrotic enterocolitis and pneumonia. A six-month old colt was given nitazoxanide for two days after which he developed a fever (101.4°F) and loose feces. The fever worsened and diarrhea developed. The colt died on Day 5 of the study. Necropsy revealed a perforated gastric ulcer and peritonitis. Another horse developed a fever (103.2°F) on Day 2 of the study, and nitazoxanide was continued despite the fever. The fever rose to 106°F, and the horse died on Day 4 of the study. Necropsy revealed granulomatous pneumonia, esophageal erosions and gastric ulcerations. A stallion developed laminitis on Day 4 of the study. and nitazoxanide was immediately discontinued. The condition persisted despite medical intervention and corrective shoeing, and the horse was euthanized two months later due to bilateral distal phalanx rotation.

Seven horses were euthanized due to insufficient recovery for work or protracted neurological disease, but necropsies were not performed. Three horses with worsening neurological conditions were euthanized and had confirmatory findings of chronic EPM on necropsy examination. One horse that was euthanized because of severe behavioral problems was diagnosed post mortem with chronic necrotizing multifocal myelitis of undetermined origin. The remaining 12 horses were euthanized (11) or died (1) as a result of other medical conditions.

e. Conclusions of Safety Studies:

The safety studies provide evidence that toxicity and death can occur at elevated doses of 45.45 mg/lb (2X the regular dose) and higher. Because the product has a narrow margin of safety, accurate dosage calculations and adherence to instructions

provided in the product labeling (package insert, client information sheet) are critical for safe use of NAVIGATOR Antiprotozoal Oral Paste.

In the field studies, three clinical signs emerged as predominant adverse reactions. Fever was observed in 13% of the treated horses. Anorexia or reduced appetite was noted in 14% of the horses. Lethargy or depression was the third common finding in the field studies and was noted in 10% of the clinical cases.

Other clinical findings included loose feces, malodorous feces, colic, diarrhea, edema, sore or warm feet, increased digital pulses, joint stiffness, joint pain, or worsening of neurological signs.

Four horses were euthanized during Field Study I due to worsening neurological signs. Twenty-eight horses died or were euthanized during Field Study II. Five of the cases were possibly associated with the use of nitazoxanide. These cases developed intractable clinical signs and were euthanized or died. The final diagnoses at necropsy included: enterocolitis, gastric ulcers, and laminitis.

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "For use in animals only. Not for use in horses intended for human consumption. Not for human use. Keep out of reach of children."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste, when administered under labeled conditions is safe and effective for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is critical for the diagnosis of equine protozoal myeloencephalitis in horses. The safe use of this product must also be monitored by the veterinarian.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

NAVIGATOR is protected under the following U.S. patent numbers:

US Patent Number	Date of expiration
5, 578, 621	September 8, 2014
5, 935, 591	January 15, 2018
5, 968, 961	May 7, 2017
6, 117, 894	May 7, 2017

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

- a. Package Insert
- b. Client Information Sheet
- c. Syringe Label
- d. Foil Pouch
- e. Dispensing Box
- f. Lid Sticker
- g. Weight Tape

disrupt the normal bacterial flora rse develops any of the loose feces, diarrhes, colic nts should be stopped ire should be initiated.

monitored for adverse on of treatment. The most itions included decreased gut alodorous and/or discolored mption, discolored urine, head

of monitoring the horse for the e made to assure adequate ing treatment with NAVIGATOR I death. For a more complete ee the Adverse Reactions section

e observed, the veterinarian mination should consist of a with a complete blood count um protein and determination of

e administration of anti-inflam-umine, DMSO, dexamethasone), Depending on the severity of the if the horse, therapy with ntil the clinical signs resolve.

ninitis while on nitazoxenide as should be used with caution in alaminitie

not be subjected to stressful se, stabling arrangements,

I to a cluster of signs consisting hargy and depressed appetite. ks of treatment. The signs are inflammation in response to the ie severity of the crisis, antiig may be continued during the ly monitored for appearance of a, colic, laminitis).

not been determined in breeding

as with compromised renal or fore, nitazoxanide must be tic and biliary disease, to horses ed renal and hepatic disease

protein-bound to plasma nen administering nitazoxanide bound drugs with narrow sites may occur.

erapies in horses has not been

ned horses diagnosed with EPM. lended dose. The following

at least one dose of enced adverse reactions as

depression were the most study. The following table

Table 1. Onset and Duration of Most Common Adverse Reactions in Field Study I

												•																
Adverse Reaction	0.	¥ o	n	48	tm)al																						
(n-enimals affected)	1	2	3	4	5	6	7	8	9	10	Ħ	12	13	14	15	16	17	妈	19	20	21	22	Z	24	25	26	7	28
Favor a=10 median duration 1 day	ľ			ŕ	53	157																						_
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Lathargy/Depression 8=7 median deration 2 days	Ş	;	8										-															ľ
Neurological Worsening E=3 modies duration 11 days*			*		F																							-
Loose Feden/Diarrhea a=2 median duration 1 day**	Ī		1.5																	Ī	r					1		l
Colic z=2 median duration 1 day***																					-							-
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	3	21	2	23	24	25	25	27	2

Two horses were euthenized after 11 and 24 days of neurological worsening, one horse improved after four days Bairs represent both affected horses; one horse had dienthee on Dey 2 and one horse had dienthee on Dey 3 "Bairs represent both affected horses; one horse was collicky on Dey 8 and one was collicky for one hour on Day 20

Aside from the adverse reactions that occurred in the horses that died or were euthanized, most of the adverse reactions were reported as isolated events. In some cases, however, certain adverse reactions occurred together. During this study, fever, lethargy/depression and anorexia/reduced appetite were reported study, tever, remargy/depression and anorexta/reduced appetite were reported to occur together in three cases. Fever and anorexia/reduced appetite were also observed concurrently with worsening of neurological signs (one case) and lethargy/depression and diarrhea (one case). In two cases, anorexia/decreased appetite was accompanied by fever and worsening of neurological signs respectively.

Of the 22 horses in Field Study I that experienced adverse reactions, six resolved without any therapeutic intervention. The clinical signs in the remaining 16 horses were treated with anti-inflammatory drugs such as dexamethasone, flunixin meglumine, phenylbutazone and DMSO. In some cases, intravenous fluids were also administered.

Four horses were euthanized during this study because of worsening neurological conditions. Three of these horses had necropsy findings consistent with chronic EPM. Two of the four also experienced adverse drug

In Field Study II, 416 horses received at least one dose of nitazoxanide. One hundred twenty-nine horses (31%) demonstrated adverse reactions as noted in the following tables.

Fever, anorexia/reduced appetite and lethargy/depression were the most commonly observed adverse reactions in this study. The following table describes the onset and duration of these adverse reactions.

Table 2. Onset and Duration of Most Common Adverse Reactions in Field Study II

Adverse Reaction	B	y c	ŧ	e,	bn		ŀ																					
(==animais allected)	T	2	3	1	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	2
Fever a=67 medias duration 2 days	2	ij	100	3	**	3	_	Γ																				
Anoresin/Reduced Appetite 8=58 median duration 4 days	1		3		Į.	1	7	5	2				-				-	9	i A	of The	Ot	d I	ior	70	7.			-
Lothargy/Depression a=39 median duration & days	24	17.	1	100	7.2		-6	ij.	ď,	E	i i						_			-	-				-	_		
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Luces Feces/Diarrhea 828 medias duration 2 days	2	T.		100	18	S.	180	327	Ŋ.	¥	Γ																	l
Colic n=\$ modian duration 2 days	l			ı	l	2														,	_							
	1	2	3	1	5	6	7	8	9	10	п	12	13	14	15	15	17	18	19	7	21	2	23	24	ă	7	27	2

During this study, anorexia/reduced appetite and lethargy/depression were concurrently reported in four cases. In three of the four cases, the clinical signs were also accompanied by loose feces/diarrhea. One febrile horse monstrated anorexia/reduced appetite along with loose feces/diarrhea, and another febrile horse had anorexia/depressed appetite with lethargy/ depression and lymphadenopathy. Other adverse reactions were reported as isolated events

Clinical signs resolved without any therapeutic intervention in 44 of the 129 horses that showed adverse reactions. The remaining 85 horses were managed with anti-inflammatory agents or combination therapy comprised of an anti-inflammatory agent and another class of drug. For example, four of 40 arriam-intermitatory agent and arrionine class of orug. For example, four of 4th horses demonstrating lethargy/depression were treated with fluminin meglumine, phenylbutazone, dexamethasone, DMSO, cettiofur and folic acid. Fever was managed in 19 of 57 horses with fluminin meglumine, phenylbutazone, dexamethasone and gentamicin. Anorexic horses received fluminin meglumine, dexamethasone, cimetidine and mineral oil in six of 59 cases. Eight of 21 horses demonstrating edema were treated with flunkin meglumine, phenyibutazone, furosemide, procaine penicillin, trimethoprim sulfa and bran mash. Six of 10 horses with increased digital pulses and sore, warm test received flumixin meglumine, phenylbutazone and topical nitroglycerine. Colic was treated with flumixin meglumine, mineral oil, bismuth subsalicytate and IV fluids in six of the eight classs. Four of nine horses demonstrating neurological worsening received flunkin meglumine, dexamethasone, DMSO, detomidine and vitamin E. Various treatment regimens (dosage and combination) were utilized, but most were administered for brief periods of time due to rapid resolution of clinical signs. No adjunctive therapy was administered to horses with loose feces or diarrhea. In addition to the previously mentioned treatments, administration of nitazoxanide was interrupted in 24 tebrile horses. The median duration that a horse did not receive nitazoxanide was two days.

Table 3. Incidence of Adverse Reactions Recorded in Field Studies I & II

Body System	Adverse Reactions	% Incidence in Field Study I (n/81)*	% incidence in Field Study II (n/416)
Total		27% (22/81)	31% (129/416)
Alimentary	Anorexia	2 (2/81)	14 (59/416)**
and Ufinary	Reduced appetite	9 (7/81)	**
	Loose feces	0 (0/81)	3 (14/416)
	Discolored urine! or	1 (1/81)	3 (12/416)
	discolored ^{††} malodoro	us urine/ieces	•
	Colic	2 (2/81)	2 (8/416)
	Diarrhea	2 (2/81)	1 (6/416)
	Hematuria, stranguria	1 (1/81)	0 (0/416)
Circulatory	Shock	0 (0/81)	<1 (1/416)
	Elevated heart rate and respiratory rate	t (1/81)	0 (0/416)
Hemolymphatic	Fever	12 (10/81)	14 (57/416)
	Edematous limbs	7 (6/81)	5 (19/416)
	Lymphadenopathy	0 (0/81)	<1 (2/416)
	Leukopenia	0 (0/81)	<1 (2/418)
	Facial edema	0 (0/81)	<1 (2/416)
	Mastitis	ó (0/81)	<1 (1/416)
Musculoskeletai	Sore/Warm feet/ Increased digital puls	1 (1/81)	2 (10/416)
	Stiffness	2 (2/81)	<1 (2/416)
	Pastern/Joint pain	0 (0/81)	<1 (1/416)
Neurological	Lethargy/Depression	9 (7/81)	10 (40/416)
	Worsening of	4 (3/81)	2 (9/418)
	neurological signs		• •
	Behavioral changes	0 (0/81)	<1 (2/416)
Respiratory	Nasal discharge	0 (0/81)	<1 (1/416)
** # h		1	

*n = # horses
** Horses with anorexia and reduced appetite were combined in this study
** Horses with anorexia and reduced appetite were combined in this study

Twenty-eight horses died or were euthanized during Field Study II. Five of these cases were possibly associated with the use of nitazoxanide and are summarized as follows: One horse became febrile (103°F) on Day 8 of the study and nitazoxanide was stopped. The fever worsened (106°F) and projectile diarrhea developed. The horse was euthanized on Day 11 of the study. Necropsy revealed acute bacterial typhlocolitis. Another horse exhibited lethargy and anorexia on Day 2 of the study, but continued to receive nitazoxanide. On Day 7 of the study, the horse developed diarrhea and on Day 8 had a fever of 104%. Despite stopping treatment and transfer to

Urine color can change from bright grange to dark vallow due to excretion of nitracoxanida in the urine TExcretion of nitezoxenide in the bile can change feces color from green to brown



Package insert



Antiprotozoal Oral Paste

For the treatment of equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona in horses. For oral use only.

CAUTION

Federal (USA) law restricts this drug to use by or on the order of a licensed

DESCRIPTION

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste is supplied in ready-to-use syringes containing 85 grams of paste. Each gram of paste contains 320 mg of nitazoxanide (32% w/w). NAVIGATOR (32% nitazoxanide) is an orally administered paste.

Each syringe of NAVIGATOR Paste contains enough paste to treat one (1) 1,200-pound horse to two (2) days at the starting dose of 11.36 mg/lb or one (1) day at the regular dose of 22.72 mg/lb body weight. The plunger is fitted with a dosage ring designed to deliver a dosage of 22.72 mg/lb and is marked for a horse weighing up to 1,200 pounds. The NAVIGATOR dispensing box contains 26 syringes; which provides sufficient paste to treat one 1,200-pound horse for 28 days (5 days at 11.36 mg/lb and 23 days at 22.72 mg/lb).

Chemical name: 2-(acetyloxy)--N-(5-nitro-2-thiazotyl) benzamide

Empirical formula: C₁₂ H₂ N₃ O₅ S

Molecular weight: 307.3

Structural formula:

INDICATIONS

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste is indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by Sarcocystls neurona.

DOSAGE & ADMINISTRATION

Always provide the Client Information Sheet to the animal owner or person treating the horse with each prescription, NAVIGATOR Paste should be administered orally once a day for 28 days as follows:

Days of Administration

Days 1-5

Target Dose

Days 6-28

11.36 mg/lb body weight 22.72 mg/lb body weight

PLEASE NOTE: A total of 26 syringes are included in the NAVIGATOR dispensing box. The three syringes in the first three spaces will be used to dose the horse for Days 1-5. The remaining 23 syringes will dose the horse for Days 6-28. The dose is 11.36 mg/lb for the first five (5) days, and 22.72 mg/lb for Days 6-28.

Nitazoxanide has not been evaluated in horses that weigh greater than 1,200 pounds,

DIRECTIONS FOR USE

Step 1 Obtain an accurate body weight periodically (once a week) to ensure the correct dose is administered. Use a scale or the weight tape provided in the NAVIGATOR dispensing box.

Step 2 Open the foil pouch and remove the NAVIGATOR syringe. Set the dosage ring for the appropriate dose according to the following schedule.

Day 1.—Use the syringe in the space marked #1 and set the dosage ring to one-half (1/2) the horse's weight in pounds.

Day 2—Use the partially used syringe from Day 1 and set the dosage ring to the <u>full weight</u> of the horse in pounds (this will deliver the same amount as administered on Day 1).

Day 3—Use the syringe in the space marked #2 and set the dosage ring to one-helf (1/2) the horse's weight in pounds.

Day 4—Use the partially used syringe from Day 3 and set the dosage ring to the <u>full weight</u> of the horse in pounds (this will deliver the same amount as administered on Day 3).

Day 5—Use the syrings in the space marked #3 and set the dosage ring to one-test (11/2) the horse's weight in pounds. Syrings #3 will be only partially used. Save this syrings until dosing is complete and then discard it along with the other syringss.

Days 6-28—Use the remaining syringes and set the closage ring to the <u>full weight</u> of the horse in pounds.

To set the dosage ring on the syringe plunger, rotate (dial) the top of the ring to the appropriate dosing mark.



Step 3 Ensure the horse's mouth contains no feed. Remove the cover from the tip of the syrings and insert the tip into the horse's mouth at the interdental space. Depress the plunger until it is stopped by the dosage ring. The dose should be deposited on the back of the tongue or deep into the cheek pouch.

Step 4 To aid swallowing of paste, immediately raise the horse's head for a few seconds after dosing.

Step 5 Clean the tip of the syringe with a clean disposable towel and replace the cover on the tip of the syringe. Return the syringe to the original space in the NAVIGATOR dispensing box.

Step 6 Repeat until the horse has been treated for 28 days. Weigh the horse weekly and set the dose based upon the current body weight to ensure accurate dosing.

Step 7 At the end of the treatment period, all empty and partially empty syringes should be discarded. Do not reuse dosing syringes.

CONTRAINDICATIONS

This product is contraindicated for use in horses less than one year of age and in horses that are sick or debilitated for reasons other than EPM.

WARNINGS

Warnings: Administration of nitazoxanide can disrupt the normal microbial flora of the gastrointestinal tract leading to enterocolitis. Deaths due to enterocolitis have been observed while administering the recommended dose in field studies.

Obtain an accurate body weight and calculate the dose weekly during treatment. Overdosing of nitazoxanide must be avoided. Read the Dosage & Administration and Precautions sections of the package insert before dosing the horse. It is important to monitor the horse for adverse clinical signs during treatment. Read the Adverse Reactions section of the package insert for more information on adverse reactions.

HUMAN WARNINGS

For use in animals only. Not for use in horses intended for human consumption. Not for human use. Keep out of reach of children.

PRECAUTIONS

Administration of nitazoxanide to horses of the gut resulting in an enteropathy. If a following: a high fever (> 103°F), scare or signs of laminitis, nitazoxanide treat immediately and appropriate veterinar

Horses on nitazoxanide treatment should reactions at least once daily for the du common adverse reactions observed wei and lethargy/depression. Other adverse t sounds, scant feces, loose faces/diarrhet feces, colic, laminitis, increased water co and/or limb edema, and weight loss.

If the horse owner or caretaker is not capt above adverse reactions, provisions shou monitoring. Failure to monitor the horse can result in serious adverse reactions discussion of adverse reactions and death of this package insert.

If any of the adverse reactions listed above should examine the horse immediately. complete physical examination in conjunc and determination of serum albumin, total body weight.

Treatment of adverse reactions may inc matory drugs (phenylbutazone, flunixin m problotic agents, antibiotics and mineral cadverse reactions and the overall condition intazoxanide may need to be discontinue

Stallions may be more prone to develor compared to mares or geldings. Nitazoxar stallions and in horses that are predispose

A horse that is receiving nitazoxanide shot situations (e.g. abrupt changes in diet, excabnormally long trailer rides, etc.).

The term "treatment crisis" has been app of worsening of neurological deficits, fever This is more common during the first two versions believed to result from central nervous system dead and/or dying protozoa. Depending confiammatory therapy may be indicated. Do "treatment crisis," providing the horse is all other adverse reactions (i.e. anorexia, diar

The reproductive safety of nitazoxanide h stallions or in breeding mares or lectating

The pharmacokinetics of nitazoxanide in h hepatic function has not been studied. The administered with caution to horses with the with renal disease, and to horses with com

The active metabolite of nitazoxanide is hig proteins; therefore, caution should be used concurrently with other highly plasma protein therapeutic indices, as competition for bing

The safety of nitazoxanide with concomitar evaluated in laboratory studies.

ADVERSE REACTIONS

Two field studies were conducted in client-Nitazoxanide was administered at the recoadverse reactions were reported.

In Field Study I, a total of 81 horses receiv nitazoxanide. Twenty-two horses (27%) exp. noted in the tables below.

Fever, anorexia/reduced appetite and lethal commonly observed adverse reactions in the describes the onset and duration of these a

ield Study I; however, a tion vize not required and a

relow:

d Study II

rees lously I for EPM	All horses that completed	_
her drugs 15=78%	the study 203/250=81%	_
15=22%	47/250=19%	

valuated as successes by res and/or a negative result y 85. Thirty-eight of the 188 nalysis had a negative result

h other medications, including oidal anti-inflammatory agents,

ed for 14 days.

lethargy were observed, and norse developed edema in in meglumine for one day, ye after treatment. No other horses returned to normal.

group were dosed as follows: roup 2, one (1) whole syringe of 8 mg/lb, 1.2X the regular dose); 3 per day for 60 days (average nges of nitazoxanide per day p 5, one (1) whole syringe of 91 mg/lb, 1.1X), then two (2) 3 8-14 (average 52.27 mg/lb, nide per day for Days 15-75 served for seven days after the

experienced any adverse

completed the study. Three study period. Four of the appetite between Days 4 and nargic at some time between rises voided loose stools. All eight horses in Group 2

es completed the study. Seven atite periodically during the es were occasionally lethargic is Group 3 horses voided loose nning on Days 4 through 64. clinical signs and died after ely. The cause of death for of the colon. Two horses losing was discontinued a pectin for 0-7 days, meglumine for 0-9 days), and therapeutic intervention.

scontinued on study Day 4 ped severe clinical signs es developed decreased hree days of the study. Four of h, during Days 2-5 of the mg/lb average daily dose y. The cause of death in all

cases was severe erosion and ulceration of the colon. The three remaining horses recovered after removal from the study on Day 4 and administration of supportive therapy for six days (lactated Ringer's, cardate, kaolin pectin); they also received a 12-day course of potentiated sulfonamide.

In Group 5, the horses were dosed with the contents of one syringe per day for one week, two syringes per day for a second week and then three syringes per day for an additional 60 days (average maximum dose 78.18 mg/lb, 3.4X). All eight horses developed decreased appetite and were periodically lethargic, beginning on Days 9-23. Five horses successfully completed this dosage regimen without therapeutic intervention. Three horses demonstrated clinical signs of drug toxicity and were removed from the study on Days 17, 23 and 31. They developed significant weight loss, anorexia, lethargy and decreased gut sounds. These three horses-recovered with supportive therapy (lactated Ringer's solution, kaolin pectin and potentiated sulfonamide). Twenty-three days later, one horse developed gastroenteritis and salmoneliosis, and died.

Hypoproteinemia was observed in horses in the higher dose groups and was likely a result of a protein-losing enteropathy. Stress leukograms were also observed in the more severely affected horses. Gross and histopathological examination of animals that died in the study clearly indicates the colon as the target tissue. In animals with severe colonic lesions, the stomach, small intestine and cecum were also affected, but to a lesser degree. No treatment-related effects on other tissues were noted in study animals.

Toxicity Study II: In this study, horses were dosed as follows: Group 1 (sham-dosed for 28 days), Group 2 (11.36 mg/lb Days 1-5, then 22.72 mg/lb Days 6-28; 1X starting and regular dose), Group 3 (22.72 mg/lb Days 1-5 then 45.45 mg/lb Days 6-28; 2X starting and regular dose). All horses were observed for seven days after the last treatment. There were eight horses in each treatment group.

All horses in all groups completed the dosing portion of the study. In Group 1 (sham-dosed), four of the horses showed decreased appetite on at least one day of the study. Three horses voided loose stools or had limb or ventral edema on at least one day of the study. Two horses voided discolored brown feces (normal color of freshly voided feces was considered to be green). Four horses produced malodorous feces during the study. Four horses had no clinical findings during the study. One horse lost weight, but the group gained an average of 43 pounds during the study.

In Group 2 (1X group), one of the horses showed decreased appetite and had limb edema occasionally during the study. Three horses voided loose feces on at least one day of the study. Two horses voided discolored brown feces. Two other horses produced malodorous feces during the study. Four horses had no clinical findings during the study. No horses lost weight, and the group gained an average of 61 pounds during the study.

In Group 3 (2X group), eight horses had decreased appetite during the study period. Five horses became lethargic during the study. All eight horses had loose and malodorous feces on at least one day during the study period. Four horses had discolored brown or black feces. Five horses developed limb or ventral edema during the study. Three horses in Group 3 developed fever for at least one day during the study period.

There was a statistically significant lymphopenia observed in Group 3 horses at mid-study, and neutrophilia at the end of the study, although all mean values remained within normal reference range. Statistical evaluation of the clinical chemistry values showed decreased serum alburnin, globulin and total protein at the end of the study, although the average alburnin levels remained within the normal reference range. Three horses in Group 3 had serum total protein and serum alburnin values below the normal reference range near the end of the study period. Urinallysis values were all within the normal reference range, but the average urine pH was significantly lower in Group 3. Water consumption in Group 3 horses was elevated prestudy and remained so throughout the study period. Three horses in Group 3 lost weight, but the group gained an average of two pounds during the study.

One horse in Group 3 developed enterocolitis at the end of the study period and was given supportive therapy including antibiotics, flunixin meglumine, kaolin pectin, IV fluids, omeprazole and carafate. It was euthanized after the end of the treatment period. Diagnostic testing, complete necropsy and histopathology revealed findings consistent with alteration of gut microflora, enterocolitis and salmonellosis in this horse.

With the exception of two horses in Group 3 that received supportive therapy (one horse treated with hydrotherapy for edema, another treated with oral electrolytes for five days) and the horse described above that developed enterocolitis, all horses finished the study without supportive therapy.

At the end of the study, the three horses in Group 3 that had detectable abnormalities consisting of low serum albumin (1/3), low serum total protein (2/3) or leukocytosis (3/3) were monitored for an additional 15 days. All three of these horses returned to normal at the end of the 15 days without therapeutic intervention.

STORAGE INFORMATION

Store below 30°C (86°F). Do not freeze.

HOW SUPPLIED

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste for horses contains 32% w/w nitazoxanide and is available in an oral-dose syringe. Each syringe contains 85 grams of paste. Each gram of paste contains 320 mg of nitazoxanide (32% w/w). Syringes are fitted with a dosage ring designed to deliver a dosage rate of 22.72 mg/lb, and is marked for a horse weighing up to 1,200 pounds. The NAVIGATOR dispensing box contains 25 syringes, which provides sufficient paste to treat one 1,200 pound horse for 28 days (five days at 11.36 mg/lb and 23 days at 22.72 mg/lb).

REFERENCE

1. Trzard IR. Veterinary Immunology. 4th ed. Philadelphia, Pa: WB Saunders; 1992:104-105, 210-211, 327-329.

Manufactured for: IDEXX Pharmaceuticals, Inc., Greensboro, NC 27410 USA

Manufactured by: PM Resources, Inc. Bridgeton, MO 63044 USA

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NADA 141-178 Approved by FDA.

Manufactured under license from Romark Laboratories, L.C. under one or more of the following U.S. patents: 5,578,621; 5,935,591; 5,968,961; and 6,117,894.

IPI/NIT/IN/21 August 2003 06-04352-00

a referral hospital, the horse died on Day 16. Necropsy revealed fibronecrotic enterocolitis and pneumonia. A six-month-old cott was given nitazoxanide for two days, after which he developed a fever (101.4°F) and loose feces. The fever worsened and diarrhea developed. The colt died on Day 5 of the study. Necropsy revealed a perforated gastric ulcer and peritonitis. Another horse developed a fever (103.2°F) on Day 2 of the study, and nitazoxanide was continued despite the fever. The fever rose to 106°F and the horse died on Day 4 of the study. Necropsy revealed granulomatous pneumonia, esophageal erosions and gastric ulcerations. A stallion developed laminitis on Day 4 of the study, and nitazoxanide was immediately discontinued. The condition persisted despite medical intervention and corrective shoeing, and the horse was euthanized two months later due to bilateral distal obstants rotation.

Seven horses were euthanized due to insufficient recovery for work or protracted neurological disease, but necropsies were not performed. Three horses with worsening neurological conditions were euthanized and had confirmatory findings of chronic EPM on necropsy examination. One horse that was euthanized because of severe behaviorial problems was diagnosed post mortern with chronic necrotizing multifocal myelitis of undetermined origin. The remaining 12 horses were euthanized (11) or died (1) as the result of other medical conditions.

To report suspected adverse reactions or for a copy of the Material Safety Data Sheet (MSDS), call 1-800-374-8006.

INFORMATION FOR CLIENT

The Client Information Sheet provides important information about EPM, the proper administration of NAVIGATOR Paste and adverse reactions that may occur. The prescribing veterinarian should discuss the Client Information Sheet with the person freating the horse when NAVIGATOR Paste is dispensed. The Client Information Sheet is fixed to the inside of the upper flap of the dispensing box and also is included as a separate sheet within the dispensing box.

CLINICAL PHARMACOLOGY

Proposed mode of action: Using *in-vitro* models, it is probable that nitazoxanide is selectively toxic for organisms capable of intracellular reduction of the nitazoxanide nitro group to a toxic free radical. This activity interferes with cellular respiration of the target organism.

Based upon cell culture data, dosages of nitazoxanide 1.0 ppm or greater prevented measurable monotayer destruction in a lesion-based microassay against *S. neurona* merozoites. In this assay, the concentration of nitazoxanide that inhibited the merozoites by 50% (inhibitory concentration 50; IC₆₀) was 0.52 ppm.

Pharmacokinetics: Eight (4 males, 4 females) mixed-breed, healthy horses received either a single dose or multiple doses of NAVIGATOR Paste for seven consecutive days. Nitazoxanide is rapidly metabolized to the active metabolite, deacetylnitazoxanide. Plasma drug levels of deacetylnitazoxanide were nondetectable by 24 hours post-dosing. The limit of detection (LOD) was 0.02 ppm.

The data from the pharmacokinetic study are presented in the following table:

Table 4. Pharmacokinetic Parameters

		ined by Single and M thy Horses (mean ± 8	
Dose (22.72 mg/lb)	C _{max} (ppm)	T _{mex} (hrs)	AUC _{elog} (ppm/hrs)
Single	0.51 ± 0.30	2.13 ± 1.13	1.913 ± 0.53
Multiple	0 97 ± 0.49	3.25 ± 3.57	4.770 ± 2.78

CMaximum concentration of deacetylridazoxaride achieved

ALIC Name—Area under the curve from time 0 through the last sample with deacely/initiazoxamide concentration above the LOQ.

Based on the $C_{\rm max}$ and AUC values of the single and multiple closes, some accumulation does occur. When comparing the individual pharmacokinetic data ($C_{\rm max}$ $T_{\rm max}$, AUC) across the study days, and based on the mean standard deviations for each value, there was intersubject variability in the rate and extent of product disposition.

The C $_{\rm max}$ for deacety/initazoxanide after multiple doses of 22.72 mg/lb was 0.97 ppm (1.9X the IC $_{\rm so}$ of 0.52 ppm). These data pradict that the concentrations of deacety/initazoxanide in the plasma would reach

therapeutic levels against *S. neurona* over the 28-day closing period. The 28-day course of therapy was selected based on the pharmacokinetics of the drug and the life cycle of the organism. The merozoites develop in a 10–14-day period after ingestion of the occysts. The 28-day course of therapy is roughly twice the length of this life cycle to help ensure that the protozoal organism is controlled before therapy is discontinued.

EFFECTIVENESS

The purpose of antiprotozoal therapy in the management of spinal cord injury associated with protozoal infestation is to kill the causative organism and arrest the progression of the disease. Horses were not expected to return to normal neurological status following treatment. It may take 12 morths or more of extensive rehabilitation to restore maximum fitness and strength. The amount of rehabilitation needed will vary according to the neuroanatomical site and severity of damage associated with the disease. The risk of permanent damage to the central nervous system increases the longer the infection continues. The damage may be temporary or permanent, which can affect the utilimate prognosis.

Field Study I:

Ninety-six horses were enrolled in the study. Forty-nine horses were included in the final analysis of effectiveness. Horses were of various breeds, ages and sexes from different geographical locations within the United States.

NAVIGATOR Paste was administered once a day for five days at 11.36 mg/lbi and then once a day for 23 days at 22.72 mg/lb. The effectiveness of NAVIGATOR Paste for treating EPM was evaluated by a standardized neurological examination and Western blot (WB) assay of the cerebral spinal fluid (CSF).

Investigators performed the neurological examination on each horse prior to initiation of dosing (Day 0), on Day 28 (last day of dosing) and Day 85 (57 days post-dosing). The Day 85 evaluation was the critical endpoint. After performing the neurological examination, the investigator assigned a grade or fraction of a grade to each horse based on the modified Mayhew scale:

- 0=no gait deficits
- 1=deficits barely perceptible, worsened with head elevation
- 2=deficits noted at a walk
- 3=deficits noted at rest and walking, nearly falls with head elevation
- 4=falls or nearly falls at normal gait
- 5=recumbent patient

All horses entered the study with a positive CSF Western blot assay for *S. neurona* and with grade 2 to 4 asymmetric spinal ataxia or grade 1 spinal ataxia if accompanied by muscle atrophy or cranial nerve deficits. In order to be considered a success by the investigator, a horse had to improve at least one grade on the modified Mayhew scale by Day 85 and/or have a negative result from a Western blot assay of the CSF by Day 85.

Based on improvement in neurological examination scores and/or a negative result using CSF Western blot assay, 28 of 49 horses (57%) were evaluated as successes. Of the 49 horses, seven (14%) had a negative result from a Western blot assay of the CSF by Day 85. Of these seven, four also had an improved neurological examination score. Twenty-two of the 49 horses (45%) were deemed to have an improved neurological examination by independent evaluation of videotapes and/or negative result from a Western blot assay of the CSF on Day 85. The table below is a summary of this effectiveness study.

Table 5. Results of Field Study i

	CSF Conversion and/or Neurological improvement	CSF Conversion on Western Blot
Clinical investigators	28/49 = 57%	7/49 = 14%
Independent evaluators	22/49 = 45%	7/49 = 14%

NAVIGATOR Paste was used concomitantly with other medications, including anthelmintics, antibiotics, nonsteroidal and steroidal anti-inflammatory agents, diuretics, tranquilizers and vaccines.

Field Study It:

Four hundred nineteen horses were enrolled in the study. Two hundred fifty horses were included in the final analysis of effectiveness. Horses were of various breeds, ages and sexes from different geographical locations within the United States.

A protocol was used for this study similar videotape record of the neurological exam CSF analysis for S. neurona was not requ

The results of the study are noted in the ta

Table 6. Results of

Study Population	Horses not previously treated for EPM with other drugs	tre
Successes	113/135=84%	
Failures	22/135=16%	

Eighty-one percent (81%) of the cases we improvement in neurological examination from the Western blot assay of the CSF by (20%) horses receiving follow-up spinal flu from the Western blot assay of the CSF.

NAVIGATOR Paste was used concomitantly anthelmintics, antibiotics, nonsteroidal and diuretics, tranquilizers and vaccines.

ANIMAL SAFETY

Tolerance Study: Eight horses were given starting dose, 5X the regular dose) and ob-

Transient depressed appetite, loose stools lasted from 11 to 14 days post-treatment. Of the legs and received supportive therapy (fit kaolin pectin for three days) beginning eight supportive therapy was administered. All eight

Toxicity Study I: In this study, eight horses Group 1, placebo (sham-dosed) for 60 days nitazoxanide per day for 60 days (average 2 Group 3, two (2) whole syringes of nitazoxanide per day for 00 days (average 110.91 mg/lb, 4.90); G nitazoxanide per day for Days 1-7 (average whole syringes of nitazoxanide per day for I 2.3X), then three (3) whole syringes of nitazoxanide per day for (2.3X), then three (3) whole syringes of nitazoxanide per day for I 2.3X). The orses were last treatment. There were eight (8) horses the streatment.

In Group 1 (placebo), none of the eight hors

In Group 2 (28.18 mg/lb, 1.2X), all eight hore horses showed no adverse reactions during horses developed a mild, transient, depress 15 of the study. Three of the horses became Day 4 and 8 of the study. Two of the Group 2 periodically between Day 6 and 36 of the student of the study from the student of th

In Group 3 (57.27 mg/lb, 2.5%), six of eight h of the horses developed a mild, depressed a study period, beginning on Day 4. All eight having the study, beginning on Day 3. Four c stools periodically during the study period, b Two of the horses in Group 3 developed sevibeing dosed for 15 days and 37 days, respebbit horses was severe erosion and uterath received supportive therapy after nitazoxanic (lactated Ringer's solution for 6-10 days, ke potentiated sufforamice for 0-3 days and flun one died. The remaining horses survived with

In Group 4 (110.91 mg/lb, 4.9X), dosing warbecause animals in this treatment group de (anorexia, diarrhea and lethargy). All eight h appetite and became lethargic during the fir the horses voided loose stools for one day c study. Five of the eight horses given the 110 died within the first two to four days of the si

T_{max}-Time maximum concentration was achieved

Client Information Sheet



This summary contains important information about NAVIGATOR Paste that you should read before administering doses to your horse. This information is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you have any questions about this information or to learn more about NAVIGATOR Paste.

1. What is EPM?

Equine protozoal myeloencephalitis (EPM) is a disease of the nervous system in horses caused by the protozoal organism *Sarcocystis neurona*. Clinical signs of EPM include loss of muscle mass, weakness and incoordination.

It is important to realize that exposure to *S. neurona* does not necessarily mean that the clinical signs of the disease will occur in the horse. It is impossible to predict which horses may display neurological signs of the disease based simply on the presence of antibodies in the blood. The development of clinical signs may depend on individual stress factors, burden of exposure, or the individual horse's immune response. A cerebral spinal fluid collection may be needed to aid in the diagnosis.

2. What is NAVIGATOR Paste and how does it work?

NAVIGATOR Paste is a 32% nitazoxanide antiprotozoal oral paste that is administered once a day for 28 consecutive days. NAVIGATOR Paste works by killing the protozoal organisms that cause the disease. A licensed veterinarian must diagnose your horse with EPM and prescribe NAVIGATOR Paste for your horse.

3. How do I determine the dosage of NAVIGATOR Paste that is correct for my horse using the weight tape?

A measuring tape designed to determine the weight of your horse has been included in every dispensing box of NAVIGATOR Paste.

To determine the weight of your horse using the weight tape:

- Wrap the tape around the girth of the horse at the level of the peak of the withers.
- 2. Pull the tape so that it depresses the flesh slightly.
- Read the weight measurement where the end of the tape meets the weight markings in pounds.

For best results, measure the horse at least three times and take an average. Use two people rather than trying to stretch your arms around the horse. Take the reading right after the horse exhales (watch nostrils or flanks).

NAVIGATOR Paste has not been evaluated in horses that weigh more than 1,200 pounds.

NAVIGATOR Paste should be administered orally once a day for 28 days as follows:

Days of Administration Days 1-5

Target Dose

Days 6-28

11.36 mg/lb body weight

22.72 mg/lb body weight

PLEASE NOTE: A total of 26 syringes are included in the NAVIGATOR dispensing both. The three syringes in the first three spaces will be used to dose the horse for Days 1–5. The remaining 23 syringes will dose the horse for Days 6–28. The dose is 11.36 mg/lb for the first five (5) days, and 22.72 mg/lb for Days 6–28.

DIRECTIONS FOR USE

- Step 1 Obtain an accurate body weight periodically (once a week) to ensure the correct dose is administered. Use a scale or the weight tape provided in the NAVIGATOR dispensing box.
- Step 2 Open the foil pouch and remove the NAVIGATOR syringe. Set the dosage ring for the appropriate dose according to the following schedule.
 - Day 1—Use the syringe in the space marked #1 and set the dosage ring to one-half (1/2) the horse's weight in pounds.
 - Day 2—Use the partially used syringe from Day 1 and set the dosage ring to the <u>full weight</u> of the horse in pounds (this will deliver the same amount as administered on Day 1).
 - Day 3—Use the syringe in the space marked #2 and set the dosage ring to one-half (1/2) the horse's weight in pounds.
 - Day 4—Use the partially used syringe from Day 3 and set the dosage ring to the <u>full weight</u> of the horse in pounds (this will deliver the same amount as administered on Day 3).
 - Day 5—Use the syringe in the space marked #3 and set the
 dosage ring to one-half (1/2) the horse's weight in pounds.
 Syringe #3 will be only partially used. Save this syringe until
 dosing is complete and then discard it along with the other
 syringes.
 - Days 6-28—Use the remaining syringes and set the dosage ring to the <u>full weight</u> of the horse in pounds.

To set the dosage ring on the syringe plunger, rotate (dial) the top of the ring to the appropriate dosing mark.



- Step 3 Ensure the horse's mouth contains no feed. Remove the cover from the tip of the syringe and insert the tip into the horse's mouth at the interdental space. Depress the plunger until it is stopped by the dosage ring. The dose should be deposited on the back of the tongue or deep into the cheek pouch.
- Step 4 To aid swallowing of paste, immediately raise the horse's head for a few seconds after dosing.
- Step 5 Clean the tip of the syringe with a clean disposable towel and replace the cover on the tip of the syringe. Return the syringe to the original space in the NAVIGATOR dispensing box.
- Step 6 Repeat until the horse has been treated for 28 days. Weigh the horse weekly and set the dose based upon the current body weight to ensure accurate dosing.
- Step 7 At the end of the treatment period, all empty and partially empty syringes should be discarded. Do not reuse dosing syringes.

Please consult your veterinarian before changing the dose.

4. What kind of results should I expect following treatment with NAVIGATOR Paste?

The purpose of antiprotozoal medication such as NAVIGATOR Paste is to kill the protozoa and to stop the progression of the disease. Horses may return to previous performance levels, but may not return to normal on a neurological examination. It may take 12 months or more for a horse to regain maximum fitness and strength. The amount of rehabilitation will vary according to the site and severity of damage to the brain and/or spinal cord. The longer the infection continues, the higher the risk of permanent damage.

5. Is NAVIGATOR Paste safe?

It is extremely important to accurately weigh the horse and dose according to that weight. It is also important to carefully monitor the horse for any adverse reactions during treatment.

In studies where NAVIGATOR Paste has been administered at the recommended dose, there have been deaths due to adverse reactions to nitazoxanide. Careful calculation of the correct dose and daily observation of the horse are essential for the safe use of the drug. Refer to Section 8 of this information sheet for further information regarding adverse reactions and monitoring your horse during treatment.

6. What precautions should I take before and during administration of NAVIGATOR Paste?

NAVIGATOR Paste should not be used in horses less than one year of age and in horses that are sick or debilitated for reasons other than EPM.

Administration of nitazoxanide to horses may induce gastrointestinal disease or result in clinical signs of laminitis (increased digital pulses, warm feet/lameness). Signs of laminitis may develop at any time during the course of treatment. Stallions are more likely to demonstrate signs of laminitis. The drug should be used with caution in stallions and in horses that are predisposed to laminitis.

Whenever possible avoid unnecessary stress to horses receiving NAVIGATOR Paste. Abrupt changes in diet, exercise, stabling arrangements, abnormally long trailer rides, and other stressful events should be avoided while treatment with NAVIGATOR Paste is in process.

The reproductive safety of nitazoxanide has not been determined in stallions or in breeding or lactating mares.

7. What information should I give my veterinarian before beginning treatment with NAVIGATOR Paste?

- Information on previous or existing serious medical conditions other than EPM.
- A list of any medications the horse is receiving, including over-the-counter drugs.
- Any dietary or nutritional supplements the horse is receiving.
- Information on the horse's diet (hay, pasture, grain, pelletized food, etc.).

8. Monitoring the Horse for Adverse Reactions and When to Contact Your Veterinarian

It is extremely important to monitor your horse while it is being treated with NAVIGATOR Paste. The treatment calendar on the inside flap of the box provides space for you to document your horse's temperature and other important clinical observations.

Take your horse's temperature prior to starting treatment to establish a baseline or "normal" temperature. Temperature readings should be taken at the same time of the day and preferably when the horse is at rest.

The horse's temperature should be taken and the daily observations performed at least once a day, before administering NAVIGATOR Paste.

Feed the horse its concentrate (grain) before administering NAVIGATOR Paste. This allows for an assessment of the horse's appetite prior to dosing.

If any of the following adverse reactions are observed, NAVIGATOR Paste should not be administered and your veterinarian should be contacted immediately:

- · Lethargy/Depression
- Anorexia
- Scant feces, loose feces, diarrhea
- · Dark or discolored urine
- Progressive weight loss
- Fever
- · Increased water consumption
- Warm/Sore feet, lameness, increased digital pulses
- Colic
- Edema of legs, face, abdomen, sheath

To report suspected adverse reactions, or for a copy of the Material Safety Data Sheet (MSDS), call 1-800-374-8006.

Manufactured for:

IDEXX Pharmaceuticals, Inc. Greensboro, NC 27410 USA

Manufactured by:

PM Resources, Inc. Bridgeton, MO 63044 USA

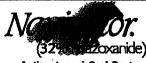
NADA 141-178

Approved by FDA.

Manufactured under license from Romark Laboratories, L.C. under one or more of the following U.S. patents: 5,578,621; 5,935,591; 5,968,961; and 6,117,894.

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Antiprotozoai Oral Paste

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Indications: NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste is indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona.

Dosage & Administration: For oral use in horses only. NAVIGATOR Paste should be administered orally once a day for 28 days as follows. Administer 11.36 mg/lb body weight for the first five days. followed by 22.72 mg/lb for the next 23 days. The dosage ring is designed to deliver a dosage rate

READ PACKAGE INSERT FOR FURTHER INSTRUCTIONS AND IMPORTANT INFORMATION.

Warnings: Administration of nitazoxanide can disrupt the normal microbial flora of the gastrointestinal tract, leading to enterocolitis. Deaths due to enterocolitis have been observed while administering the recommended dose in field studies.

Obtain an accurate body weight and calculate the dose weekly during treatment. Overdosing of nitazoxanide must be avoided. Read the Dosage & Administration and Precautions sections of the package insert before dosing the horse. It is important to monitor the horse for adverse clinical signs during treatment. Read the Adverse Reactions section of the package insert for more information on adverse reactions.

Human Warnings: For use in animals only. Not for use in horses intended for human consumption. Not for human use. Keep out of reach of children.

Storage: Store below 30°C (86°F). Do not freeze.

Manufactured for: IDEXX Pharmaceuticals, Inc. Greensboro, NC 27410 USA

Greensboro, NC 27410 USA

Manufactured by: PM Resources, Inc.
Bridgeton, MO 63044 USA

NET WT. 85 g (27 g of ritszoxanide)

Manufactured under license from Romark Laboratories, L.C. under one or more of the following patents: 5,678,621; 5,965,891; 5,898,991; and 6,117,894.

NAVIGATOR is a registered trademark of IDEXX Pharmaceuticals, Inc.

9 2003 IDEX Pharmaceuticals, Inc.

IPVNIT/SYR/15 July 2003 04-03994-02 NADA 141-178

See end of plunger for lot number and expiration date.



4.5W x 4.437H

Magenta

Black

Cyan

Pantone 294 CV

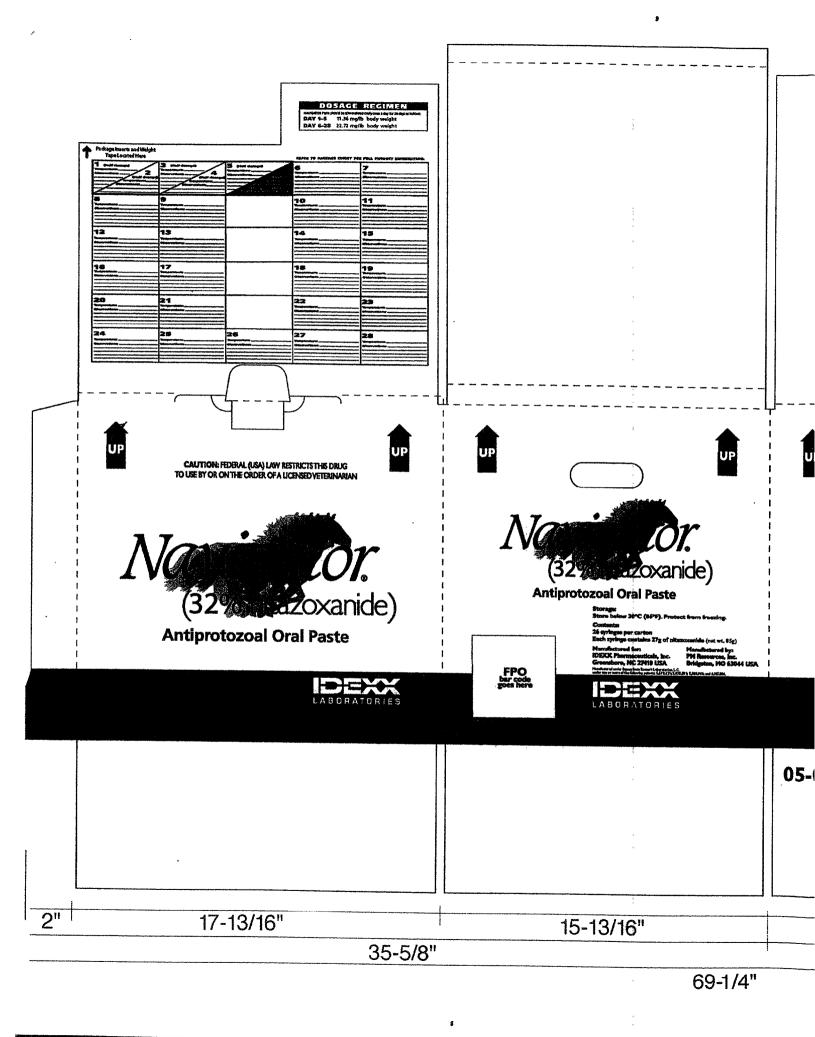


Antiprotozoal Oral Paste

IPI/NIT/FP/4 7/03 05-06934-02

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R® (32% nitazoxanide) Antiprotozoal te is Indicated for the Treatment of Equine Protozoal Myeloencephalitis 'Caused by Sarcocystis neurona.

(USA) law restricts this drug to use by or on the order of a licensed veterinarian.

g to the <u>full weight</u> i on Day 3).

Whenever possible avoid unnecessary stress to horses receiving NAVIGATOR Paste. Abrupt changes in diet, exercise, stabling arrangements, abnormally long trailer rides, and other stressful events should be avoided while treatment with NAVIGATOR Paste is in process.

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The reproductive safety of nikazoxanide has not been determined in stallions or in breeding or lactating mares.

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7. What information should I give my veterinarian before beginning treatment with NAVIGATOR Paste?

- Information on previous or existing serious medical conditions other than EPM.
- . A list of any medications the horse is receiving, including over-the-counter drugs.
- · Any dietary or nutritional supplements the horse is receiving.
- · Information on the horse's diet (hay, pasture, grain, pelletized food, etc.)

8. Monitoring the Horse for Adverse Reactions and When to Contact Your Veterinarian

It is extremely important to monitor your horse while it is being treated with NAVIGATOR Paste. The treatment calendar on the inside flap of the box provides space for you to document your horse's temperature and other important clinical observations.

Take your horse's temperature prior to starting treatment to establish a baseline or 'normal' temperature.

If the syringe and unger until it is

The horse's temperature should be taken and the daily observations performed at least once a day, before administering NAVIGATOR Paste.

Feed the horse its concentrate (grain) before administering NAVIGATOR Paste. This allows for an assessment of the horse's appetite prior to dosing.

If any of the following adverse reactions are observed, NAVIGATOR Paste should not be administered and your veterinarian should be contacted immediately:

Lethargy/Depression

• Feve

e Anomyia

· Increased water consumption

· Scant feces, loose feces, diarrhea

Warm/Sore feet, lameness, increased digital pulses

Dark or discolored urine

• Colid

· Progressive weight loss

• Edema of legs, face, abdomen, sheath

To report suspected adverse reactions, or for a copy of the Material Safety Data Sheet (MSDS), call 1-800-374-8006.

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Mariutactured under license from Romark Laboratories, L.C. under one or more of the following U.S. patents: 5,578,821; 5,935,591, 5,988,991, and 8,117,894

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NAVIGATO Oral Pas Horses with (EPM,

Caution: Feder

Antiprotozoal Oral Paste

This summary contains important information about NAVIGATOR Paste that you should read before administering doses to your horse. This information is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you have any questions about this information or to learn more about NAVIGATOR Paste.

1. What is EPM?

Equine protozoal myeloencephalitis (EPM) is a disease of the nervous system in horses caused by the protozoal organism Sercocystis neurona. Clinical signs of EPM include loss of muscle mass, weakness and incoordination.

It is important to realize that exposure to *S. neurona* does not necessarily mean that the clinical signs of the disease will occur in the horse. It is impossible to predict which horses may display neurological signs of the disease based simply on the presence of antibodies in the blood. The development of clinical signs may depend on individual stress factors, burden of exposure, or the individual horse's immune response. A cerebral spinal fluid collection may be needed to aid in the diagnosis.

2. What is NAVIGATOR Pasts and how does it work?

NAVIGATOR Paste is a 32% nitazoxanide antiprotozoal oral paste that is administered once a day for 28 consecutive days. NAVIGATOR Paste works by killing the protozoal organisms that cause the disease. A licensed veterinarian must diagnose your horse with EPM and prescribe NAVIGATOR Paste for your horse.

How do I determine the dosage of NAVIGATOR Paste that is correct for my horse using the weight tape?

A measuring tape designed to determine the weight of your horse has been included in every dispensing box of NAVIGATOR Paste.

To determine the weight of your horse using the weight tape:

- 1. Wrap the tape around the girth of the horse at the level of the peak of the withers.
- 2. Pull the tape so that it depresses the flesh slightly.
- 3. Read the weight measurement where the end of the tape meets the weight markings in pounds.

For best results, measure the horse at least three times and take an average. Use two people rather than trying to stretch your arms around the horse. Take the reading right after the horse exhales (watch nostrils or flanks).

NAVIGATOR Paste has not been evaluated in horses that weigh more than 1,200 pounds. If your horse weighs more than 1,200 pounds, do not dose with additional drug.

NAVIGATOR Paste should be administered orally once a day for 28 days as follows:

Days of Administration

Target Dose

Days 1-6

11.36 mg/lb body weight

Days 6-28

22.72 mg/lb body weight

PLEASE NOTE: A total of 26 syringes are included in the NAVIGATOR dispensing box. The three syringes in the first three spaces will be used to dose the horse for Days 1–5. The remaining 23 syringes will dose the horse for Days 6–28. The dose is 11.38 mg/lb for the first five (5) days, and 22.72 mg/lb for Days 6–28.

DIRECTIONS FOR USE

- Step 1 Obtain an accurate body weight periodically (once a week) to ensure the correct dose is administered. Use a scale or the weight tape provided in the NAVIGATOR dispensing box.
- Step 2 Open the foil pouch and remove the NAVIGATOR syringe. Set the dosage ring for the appropriate dose according to the following schedule.
 - Day 1—Use the syringe in the space marked #1 and set the dosage ring to one-half (1/2) the horse's weight in pounds.
 - Day 2—Use the partially used syrings from Day 1 and set the dosage ring to the <u>full weight</u> of the horse in pounds (this will deliver the same amount as administered on Day 1).
 - Day 3—Use the syringe in the space marked #2 and set the dosage ring to one-helf (1/2)
 the horse's weight in pounds.

- Day 4—Use the partially used syringe from Day 3 and set the dosage of the horse in pounds (this will deliver the same amount as administer
- Day 5.—Use the syringe in the space marked #3 and set the dosage n the horse's weight in pounds. Syringe #3 will be only partially used. So dosing is complete and then discard it along with the other syringes.
- Days 6-28—Use the remaining syringes and set the dosage ring to the horse in pounds.

To set the dosage ring on the syringe plunger, rotate (dial) the top of the dosing mark.



- Step 3 Ensure the horse's mouth contains no feed. Remove the cover from the tinsent the tip into the horse's mouth at the interdental space. Depress the stopped by the dosage ring. The dose should be deposited on the back into the cheek pouch.
- Step 4 To aid swallowing of paste, immediately raise the horse's head for a few s
- tep 5 Clean the tip of the syringe with a clean disposable towel and replace the syringe. Return the syringe to the original space in the NAVIGATOR dispa
- Step 6 Repeat until the horse has been treated for 28 days. Weigh the horse were based upon the current body weight to ensure accurate dosing.
- Step 7 At the end of the treatment period, all empty and partially empty syringes Do not reuse dosing syringes.

Please consult your veterinarian before changing the dose.

4. What kind of results should I expect following treatment with NAVIGATOR P

The purpose of antiprotozoal medication such as NAVIGATOR Paste is to kill the pr progression of the disease. Horses may return to previous performance levels, but normal on a neurological examination. It may take 12 months or more for a horse to fitness and strength. The amount of rehabilitation will vary according to the site and the brain and/or spinal cord. The longer the infection continues, the higher the risk

5. Is NAVIGATOR Paste safe?

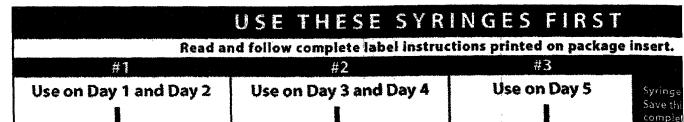
It is extremely important to accurately weigh the horse and dose according to important to carefully monitor the horse for any adverse reactions during treat

In studies where NAVIGATOR Paste has been administered at the recommended dideaths due to adverse reactions to nitazoxanide. Careful calculation of the correct cobservation of the horse are essential for the safe use of the drug. Refer to Section sheet for further information regarding adverse reactions and monitoring your horse

6. What precautions should litake before and during administration of NAVIGA NAVIGATOR Paste should not be used in horses less than one year of age and in highlighted for reasons other than EPM.

Administration of nitazoxanide to horses may induce gastrointestinal disease or rest laminitis (increased digital pulses, warm feet/lameness). Signs of laminitis may deve the course of treatment. Stalliohs are more likely to demonstrate signs of laminitis. I used with caution in stallions and in horses that are predisposed to laminitis.

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